

Clinical impact of resistance from the hospital perspective

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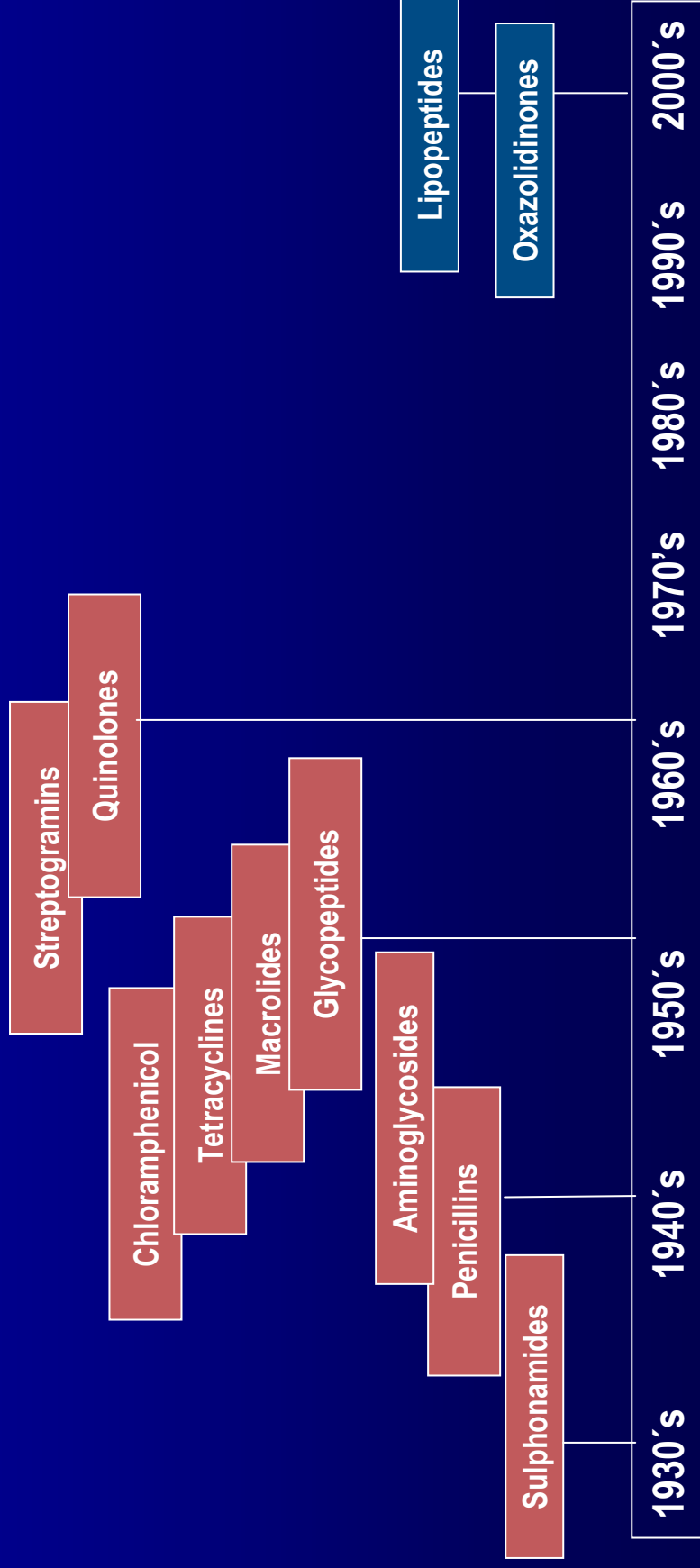
21 January 2008

Multiple antibiotic resistance

1959 *Staphylococcus aureus*, Seattle

- 40% staphylococci resistant to 4 or more antibiotics
- 85% resistant to penicillin and streptomycin
- 60% resistant to tetracycline
- 43% resistant to erythromycin
- 28% resistant to chloramphenicol

Introduction of New Antibiotic Classes



Antimicrobial resistance - the main concerns

Hospital

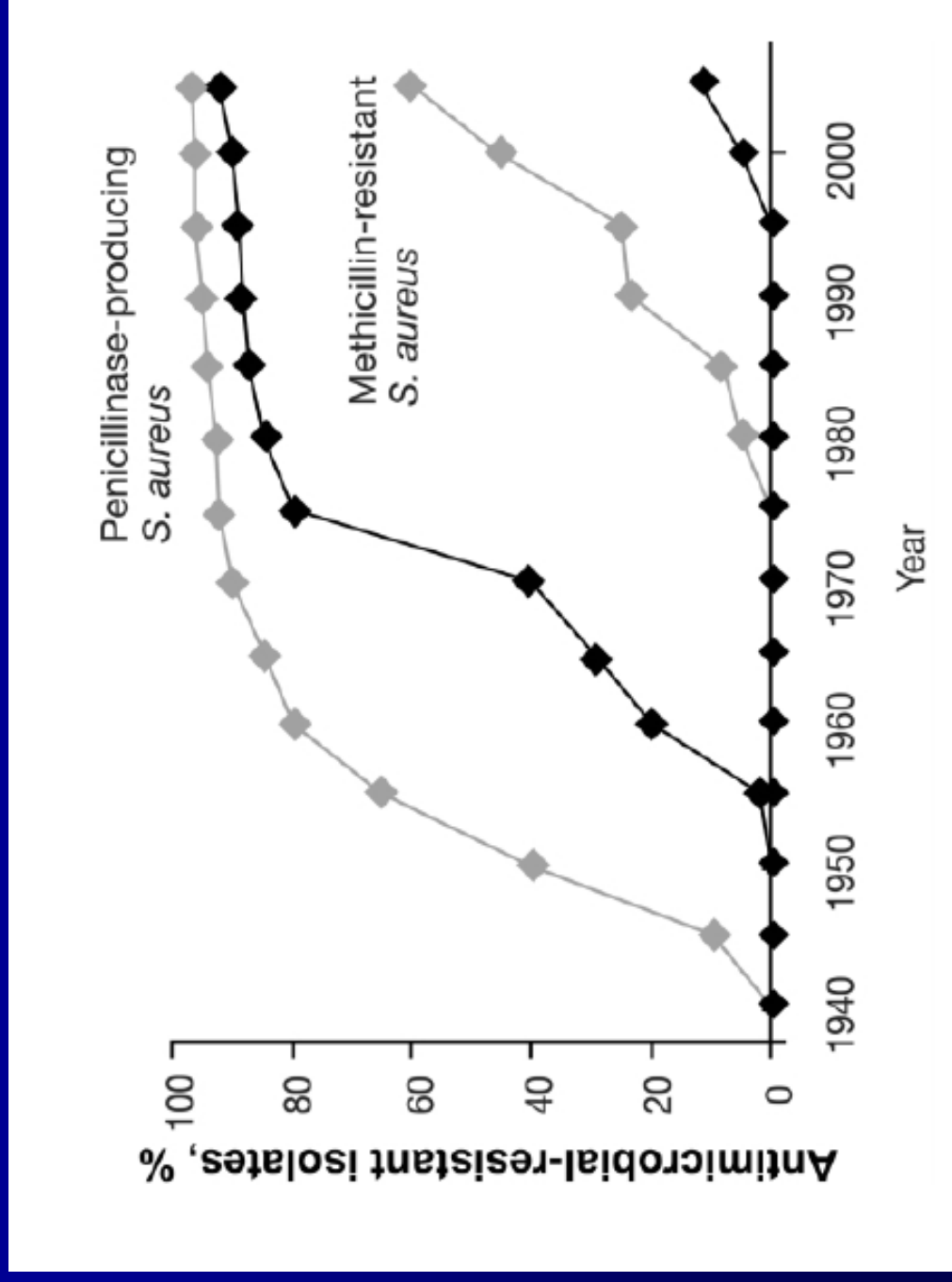
- MRSA
- VRE
- Enterobacteriaceae with extended spectrum β -lactamases (ESBL)
- *P. aeruginosa*
- *S. maltophilia*
- *Acinetobacter*



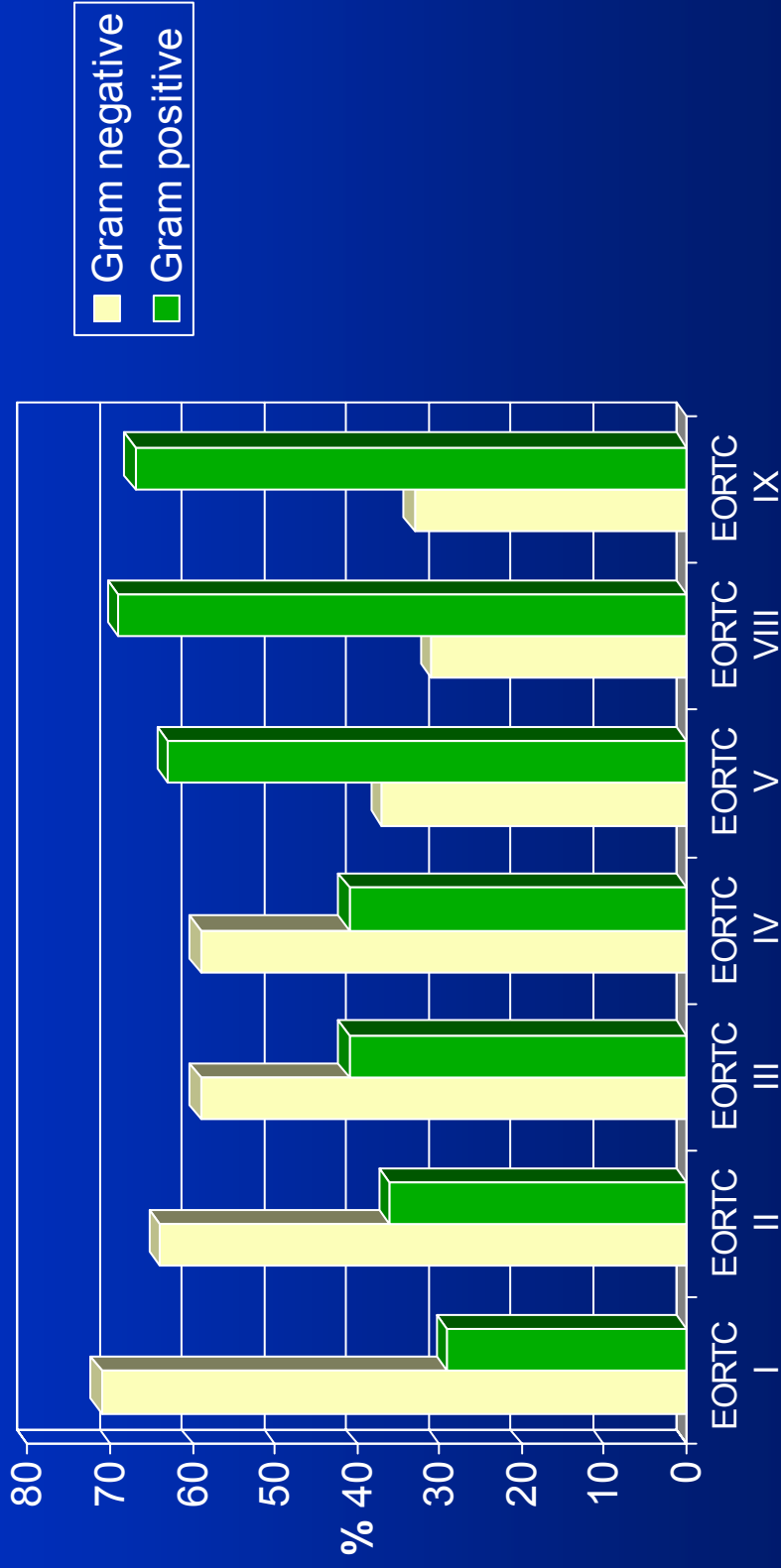
Community

- *M. tuberculosis*
- *N. gonorrhoeae*
- *S. pneumoniae*
- salmonella
- Group A streptococci
- CA-MRSA

Evolution of resistance in *Staphylococcus aureus* in hospital (grey line) and then community (black line)

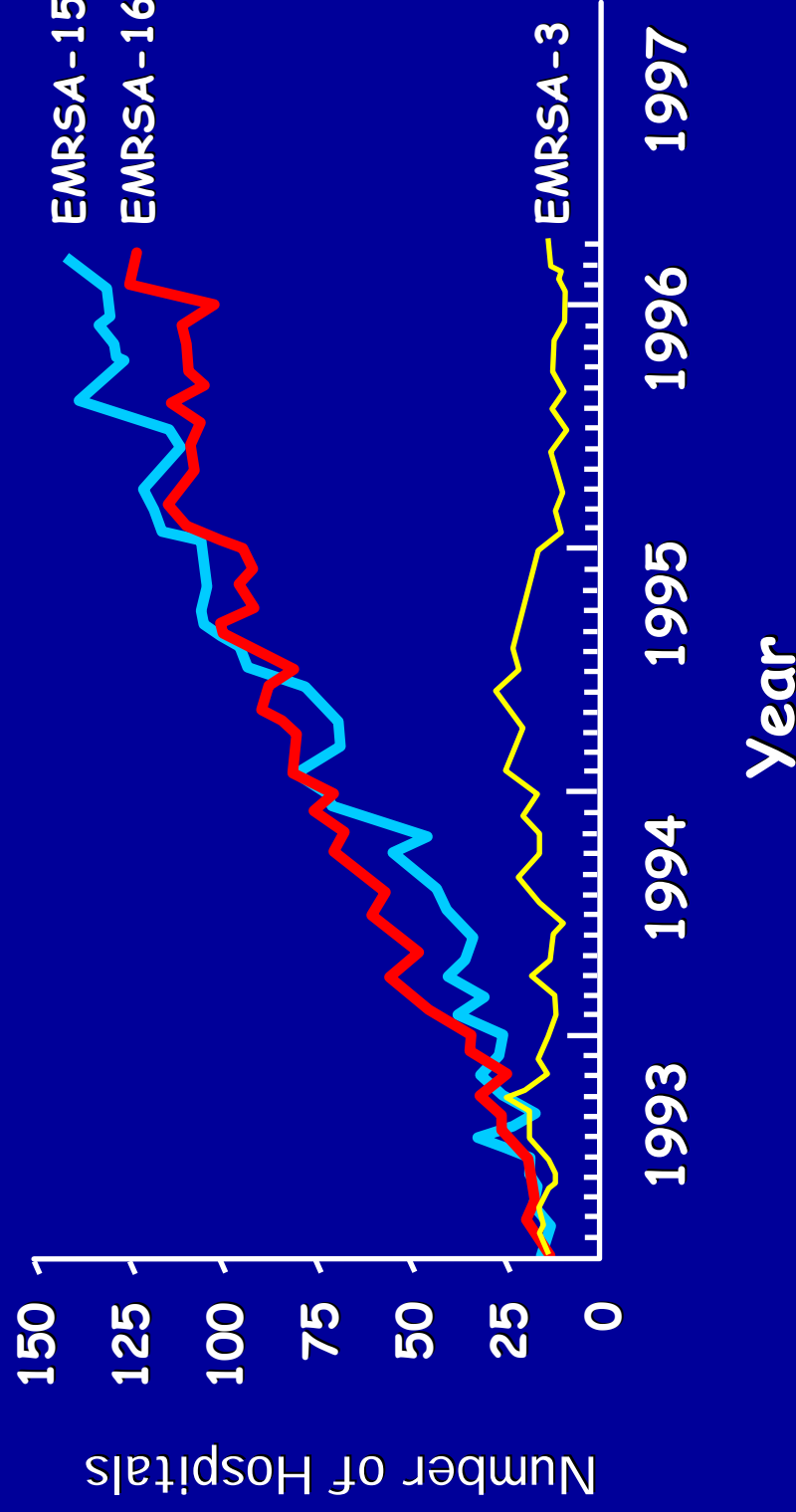


Micro-organisms isolated from blood in various EORTC trials 1973-1993



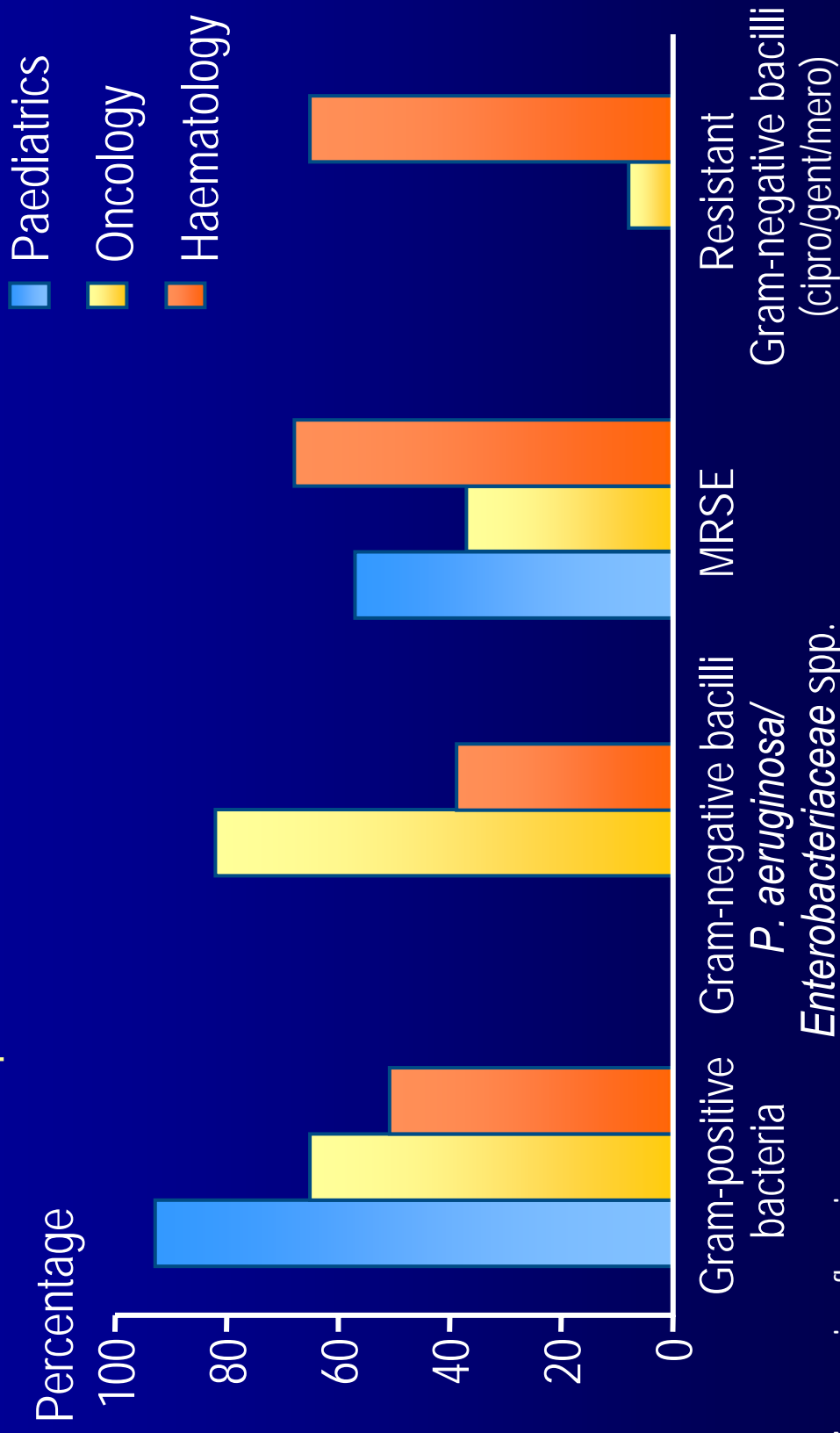
EORTC = European Organisation for Research and Treatment of Cancer

Hospitals affected by EMRSA-3, EMRSA-15, or EMRSA-16 (England and Wales)



Know your 'local' pathogen

Febrile neutropenia blood culture isolates



cipro = ciprofloxacin

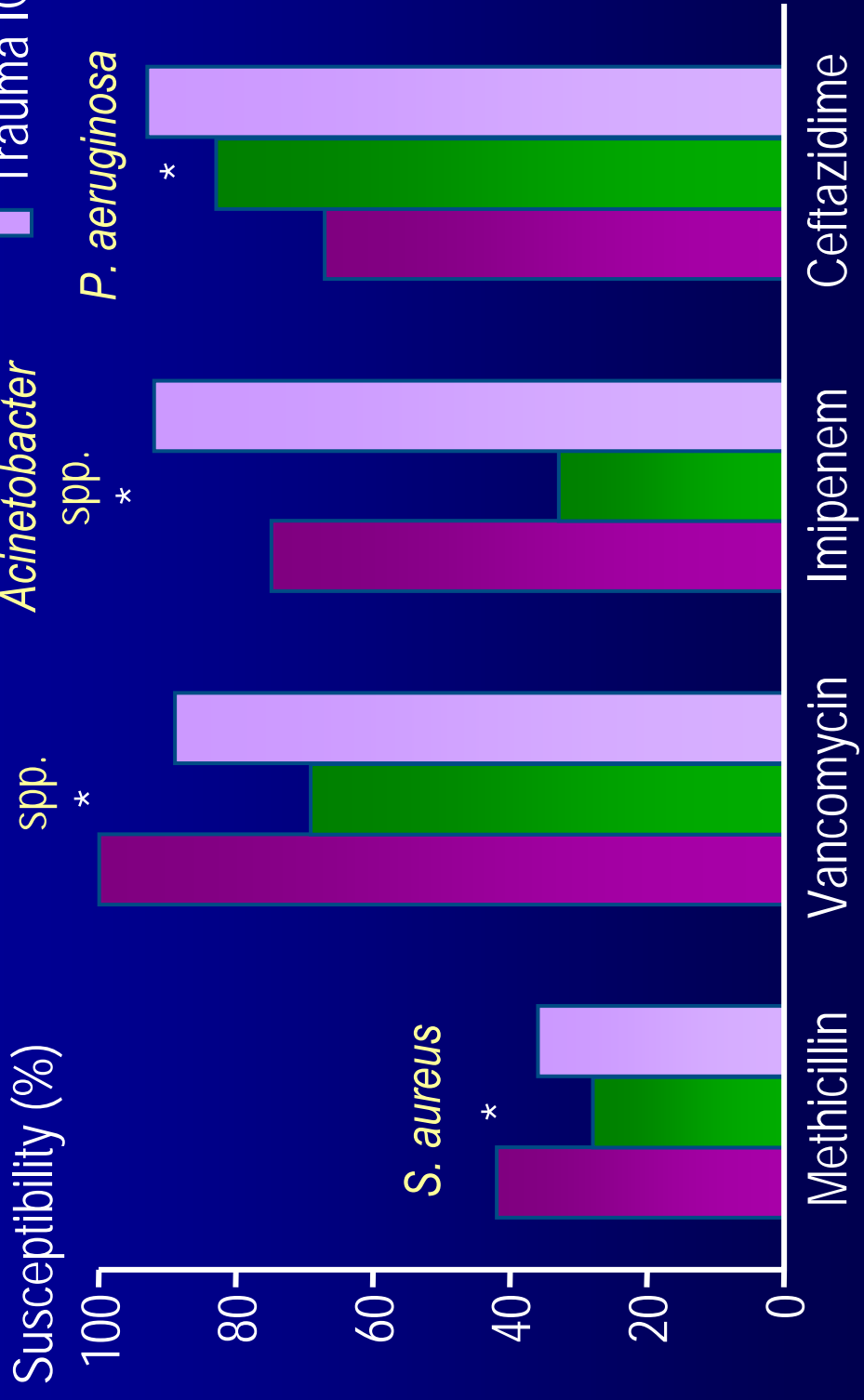
gent = gentamicin

mero = meropenem

MRSA = methicillin-resistant *S. aureus*

O'Connell et al. J Antimicrob Chemother 1998; 42: 677-678

Know your 'local' pathogen



*Significant difference between ICUs

Limitations of current antibiotic prescribing

- Remains empirical
- Diagnostic uncertainty compounded by antibiotic resistance
- Potential consequences
 - wrong organism targeted
 - wrong antimicrobial agent selected
 - unnecessary exposure to side effects
 - expenditure without benefit

Antibiotic prescribing in US hospitals

Reference	Patients	% given antibiotics	% thought inappropriate
Scheckler (1970)	5256	30.6	62
Moody (1972)	566	23	47.7
Roberts (1972)	1035	32.8	65.6
Kunin (1973)	795	28.3	51.5
Castle (1977)	1000	34.2	64

Inappropriate antibiotic therapy

Inappropriate antibiotic therapy can be defined as one or more of the following:

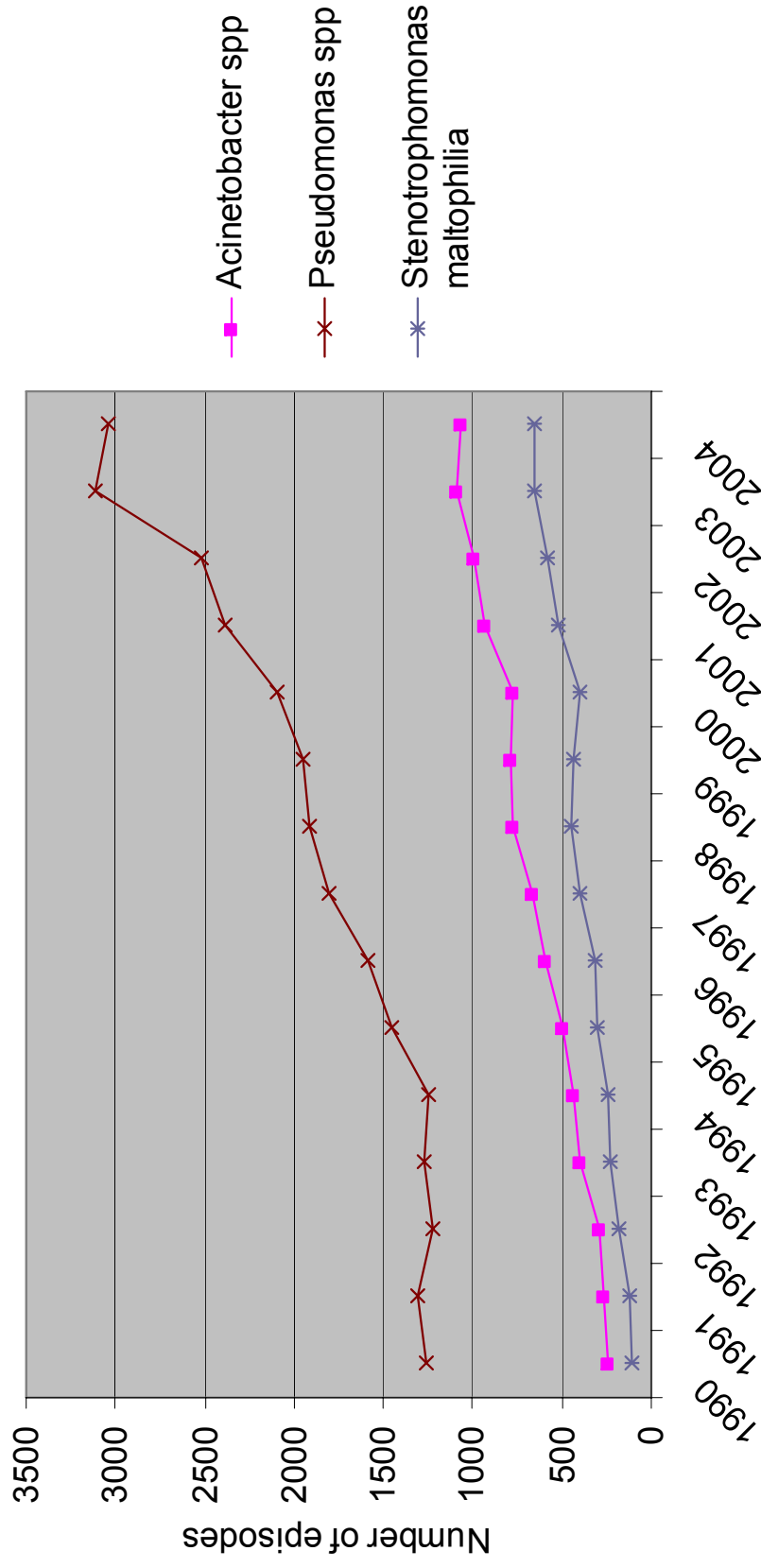
- ineffective empiric treatment of bacterial infection at the time of its identification
- the wrong choice, dose or duration of therapy
- use of an antibiotic to which the pathogen is resistant

Potential consequences of inappropriate antibiotic therapy

Inappropriate empiric antibiotic therapy can lead to increases in:

- mortality
- morbidity
- length of hospital stay
- cost
- resistance selection

Voluntary surveillance of selected bloodstream infections in England and Wales



Source: Health Protection Agency

Selected antimicrobial resistance rates from ICU infections reported to the US National Nosocomial Infection Surveillance Scheme (NNIS)

Vancomycin/enterococci
 Methicillin/*S. aureus*
 Methicillin/CNS
 3rd Ceph/*E. coli*^{***}
 3rd Ceph/*K. pneumoniae*^{***}
 Imipenem/*P. aeruginosa*
 Quinolone/*P. aeruginosa*
 3rd Ceph/*P. aeruginosa*
 3rd Ceph/*Enterobacter* spp.



■ January through December 2003
 ■ 1998 through 2002 (+/- standard deviation)[#]

Jan-Dec 2003 No. of Isolates	% increase in resistance (2003 vs 98-02*)
2048	12%
4100	11%
3336	1%
1355	0%
1068	47%
1392	15%
1825	9%
2119	20%
1411	-6%

What impact has resistance had on prescribing practice ?

Infection/pathogen

Changing regimens

urinary

sulphonamide → trimethoprim → quinolone

meningitis

chloramphenicol → ceftriaxone

gall bladder

ampicillin → cephalosporins

typhoid fever

chloramphenicol → ampicillin → quinolone

gonorrhoea

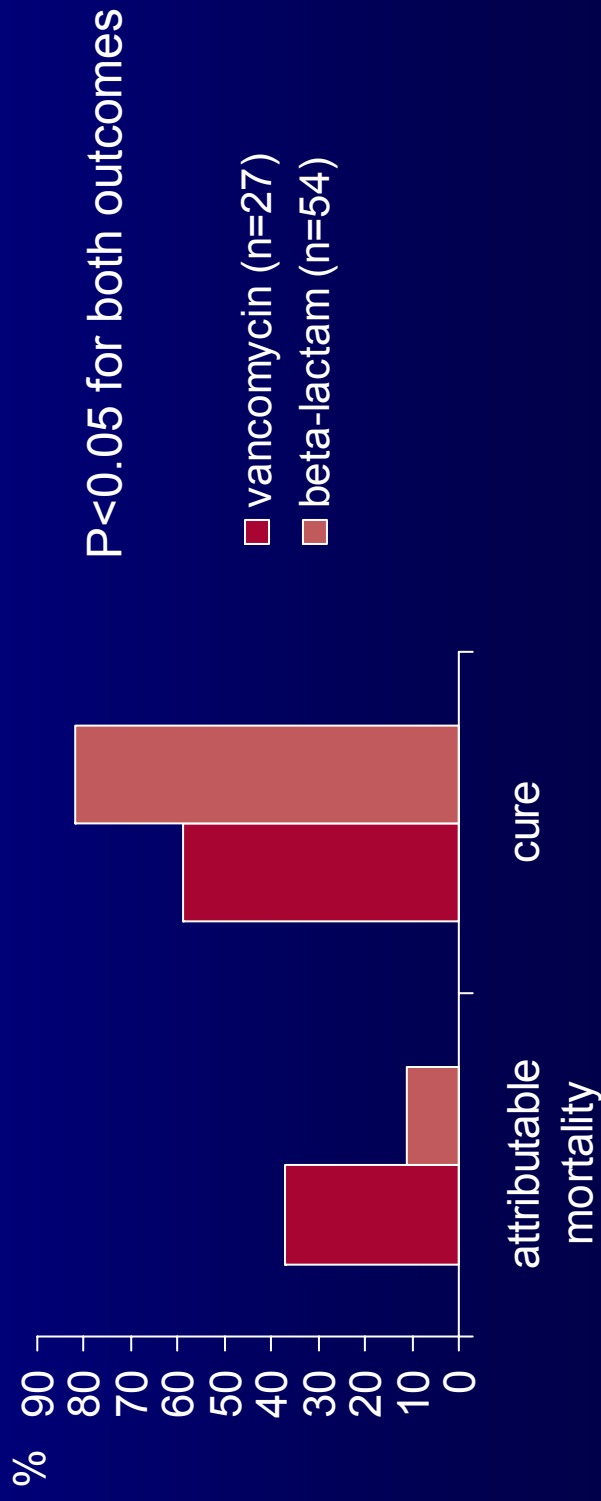
penicillin → quinolone → ceftriaxone/cefixime

staphylococci

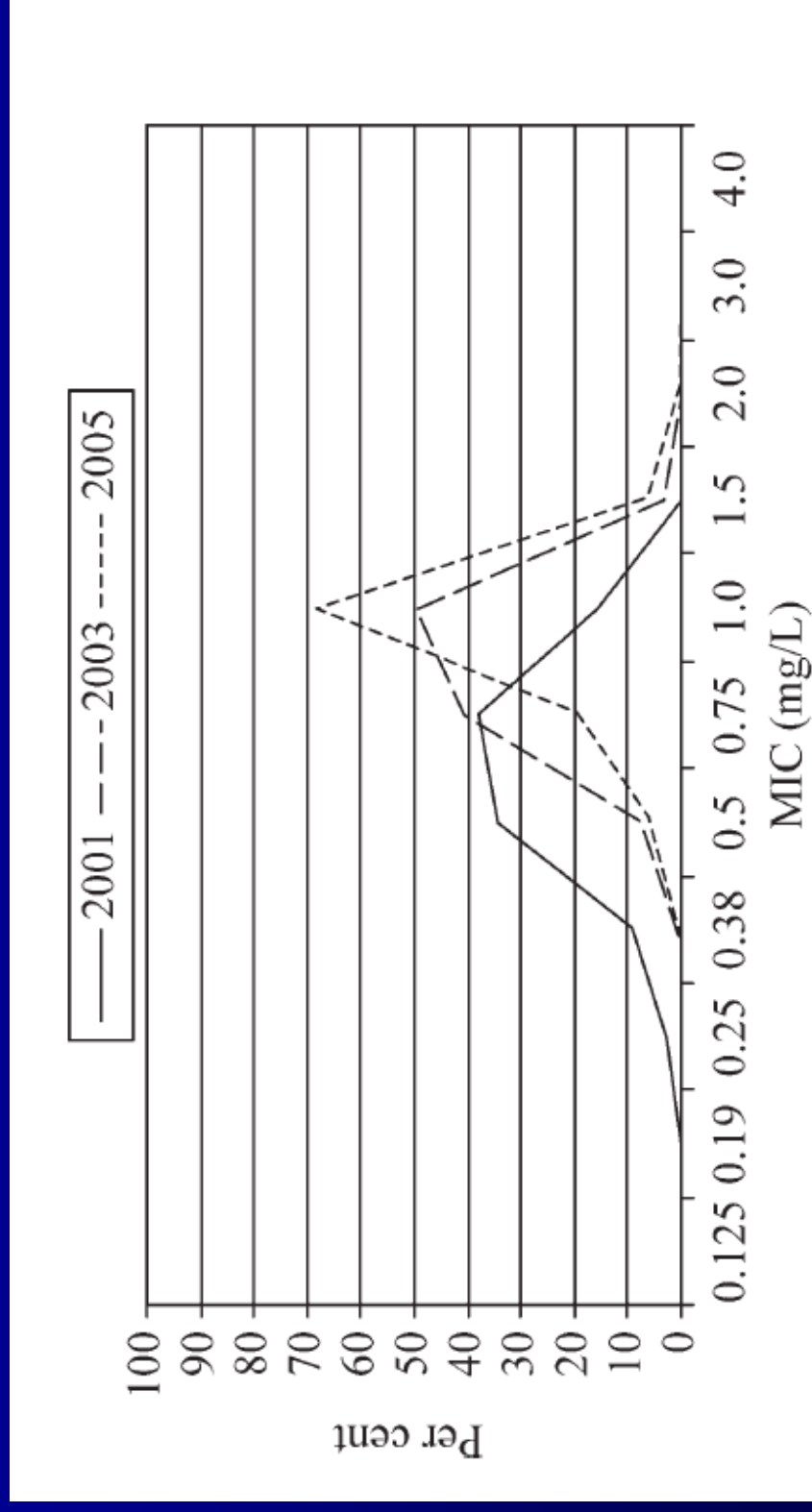
penicillin → flucloxacillin → vancomycin

Poorer outcome in methicillin-sensitive *Staphylococcus aureus* bacteraemia treated with vancomycin

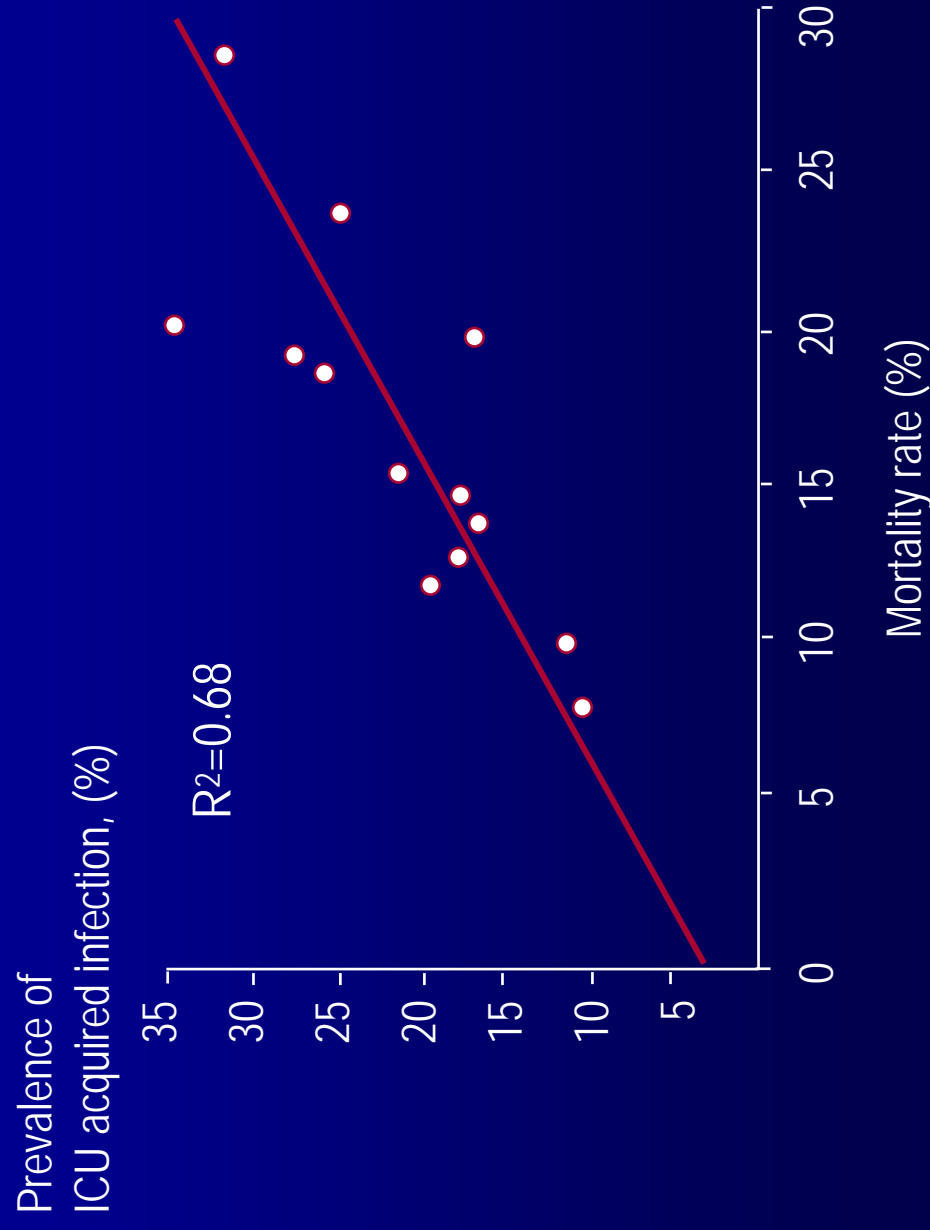
- Retrospective matched (1:2) case control study
- 27 vancomycin treated vs. 54 beta-lactam treated
- Matched for age, sex, severity of underlying illness, main underlying disease and length of hospital stay



Vancomycin MIC 'creep' in *Staphylococcus aureus* bacteraemia isolates (n=662)

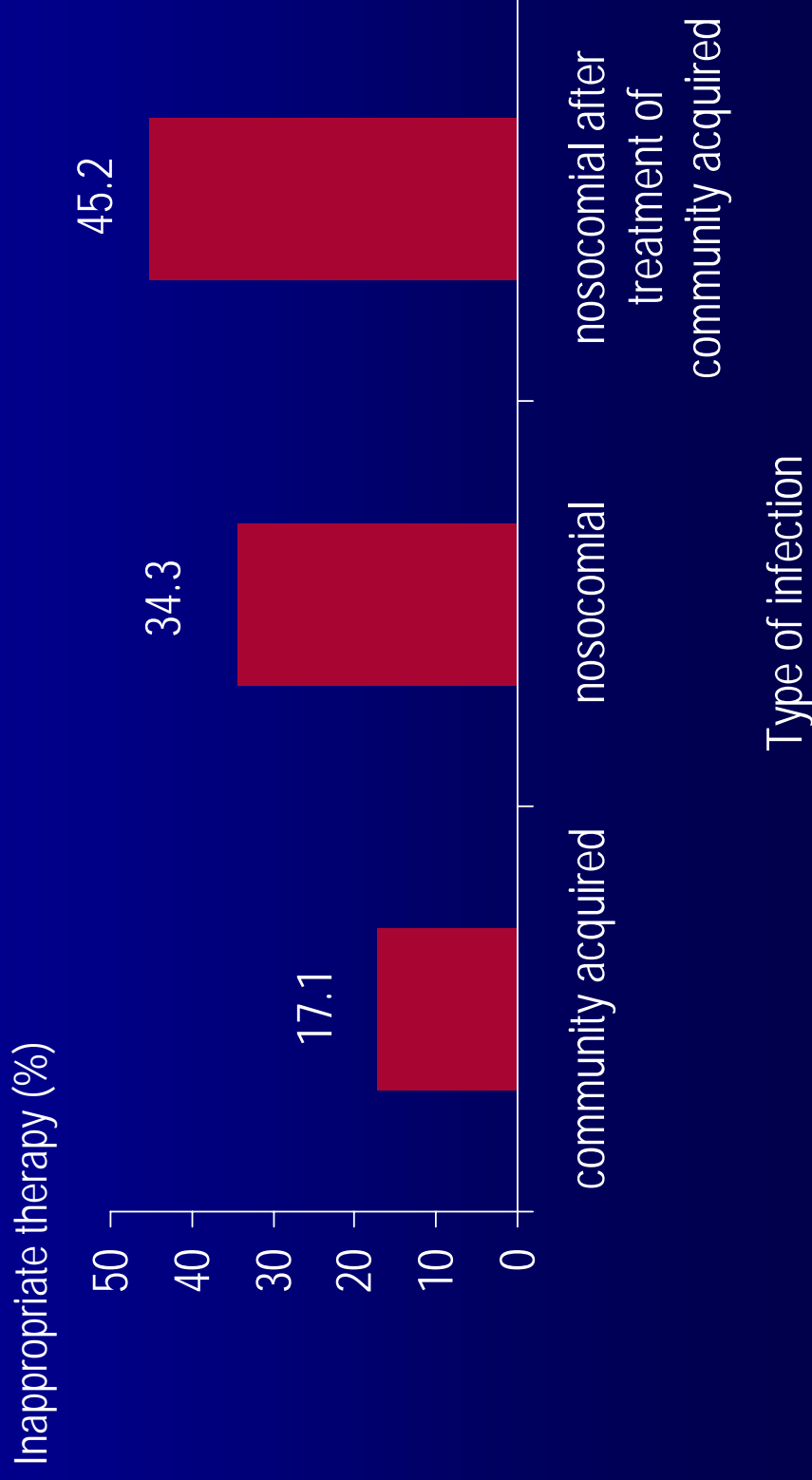


Death and infection

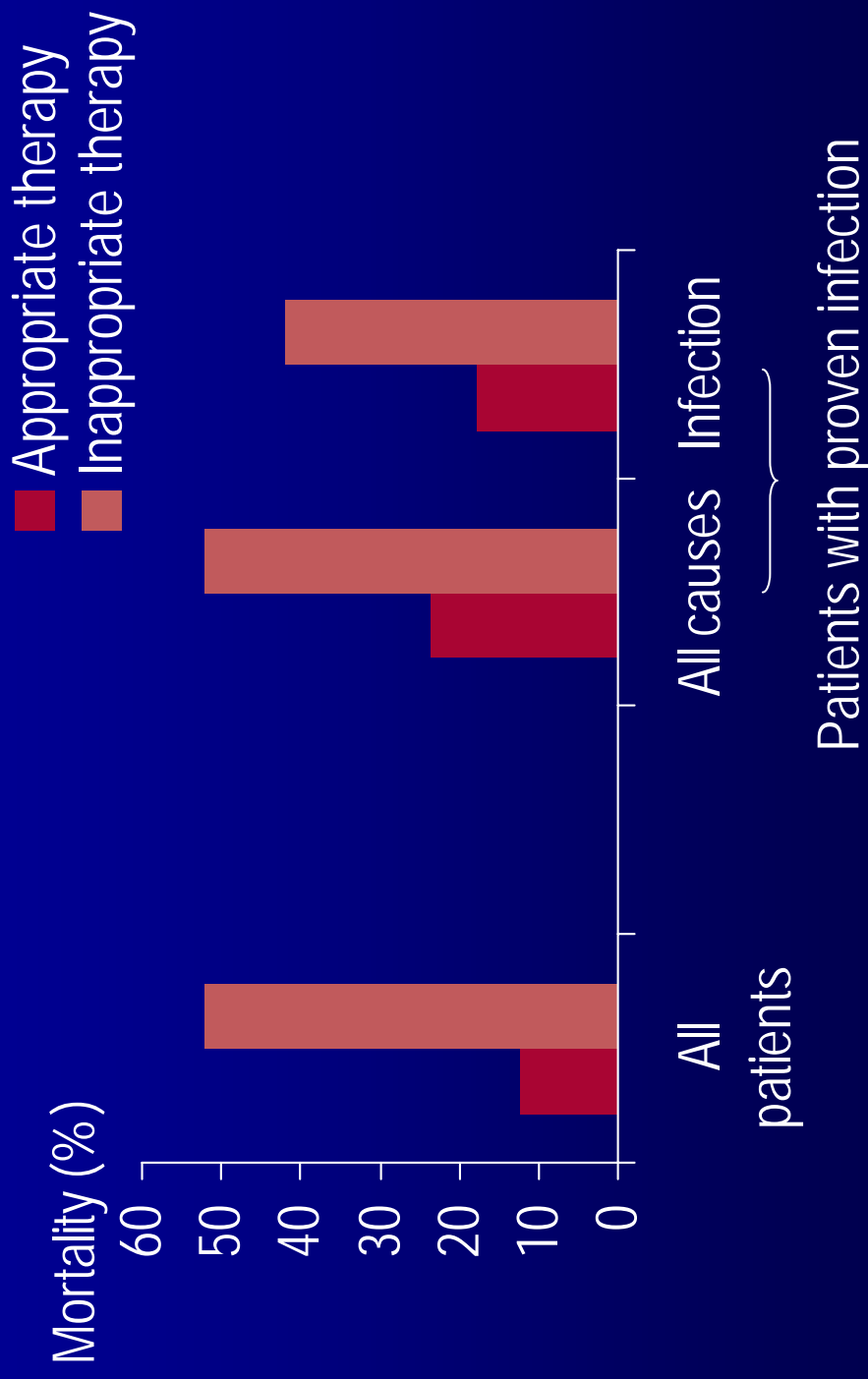


Inappropriate antibiotics cause death

Prospective study on 2,000 patients in Intensive Care
655 patients with infections



Inappropriate antibiotics cause death

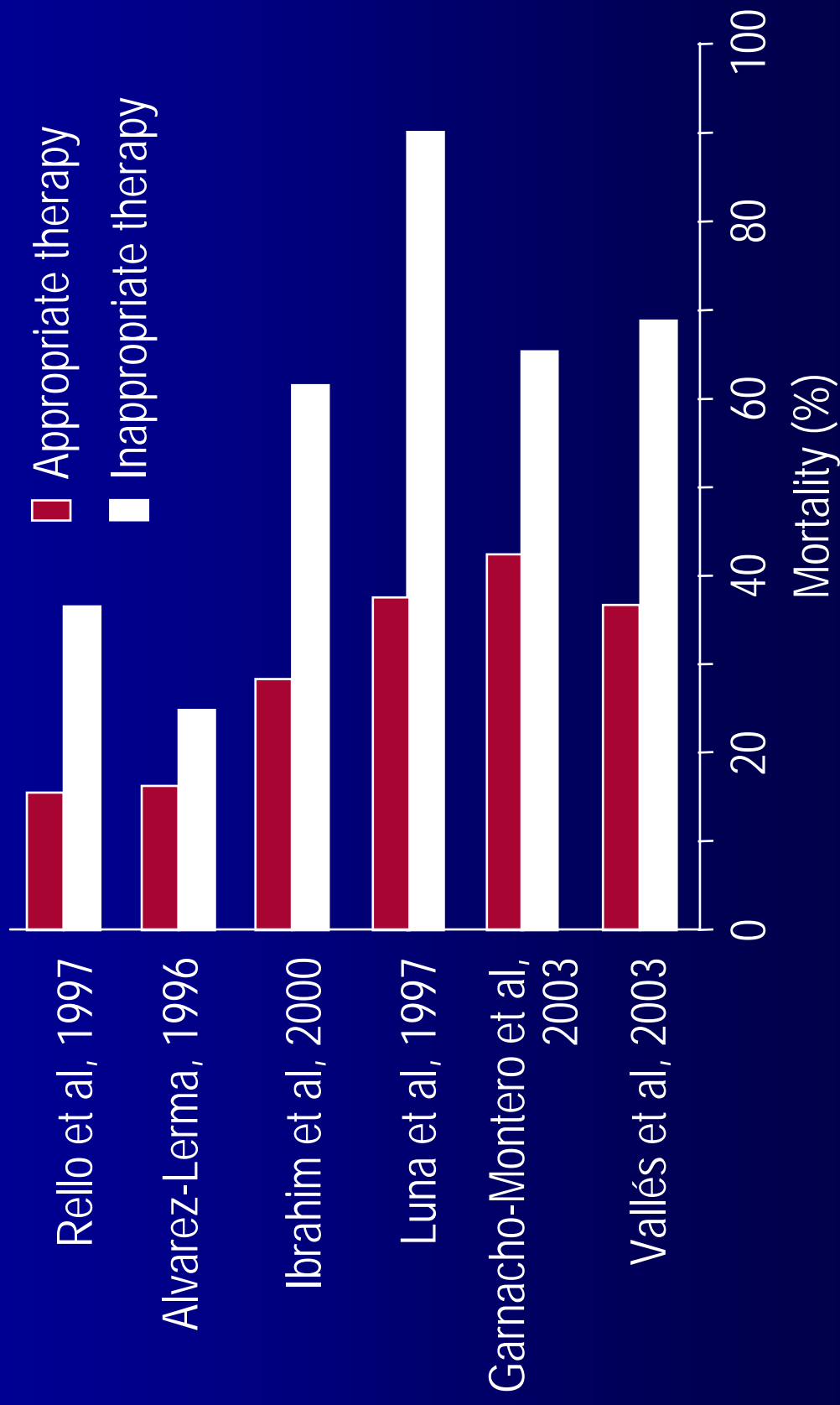


All groups $P < 0.001$

Reasons for inappropriate therapy

- Gram negative bacilli resistant to cephalosporins
- Gram negative bacilli resistant to others
- MRSA not treated
- Candida sp. not treated
- GRE not treated
- No antibiotic given

Inappropriate antibiotics cause death



MRSA bacteraemia and mortality

- Meta-analysis of studies 1980-2000
- 31 cohort studies 3,963 patients 34% MRSA
- Increased mortality with MRSA bacteraemia (OR 1.93 P<0.001)
- Consistent even when potential confounding factors were explored:
 - Proportion of nosocomial infections
 - Presence of outbreak vs. no outbreak
 - Proportion of line-associated infections
 - Proportion of infections due to endocarditis

Gram-negative resistance and outcome

Cephalosporin resistant
Enterobacteriaceae

8 studies impact
6 no impact

↑ LOS ↑ costs
↑ mortality in BSI due to ESBL

MDR *P.aeruginosa*
(≥4 agents)

6 studies impact
1 no impact

↑ mortality ↑ LOS
Variety of nosocomial infections

Carbapenem resistant
Acinetobacter

6 studies impact

↑ Mortality in BSI and ICU and burns
↑ LOS ↑ costs

Why doesn't resistance always result in a demonstrable impact on patient outcome?

- Study design
- Susceptibility testing issues
- Degree of resistance / resistance mechanism
- Spectrum of disease severity studied
- Colonisation versus infection
- Suboptimal dosing (PK/PD issues)
- Significant response in the absence of antibiotic

Resistance and outcome

Good correlation

Less good correlation

Blood stream infection

Non-bacteraemic infection

ICU

S. pneumoniae

MRSA

VRE

ESBL *Enterobacteriaceae*

MDR *P. aeruginosa*

carbapenem-resistant *Acinetobacter*

Summary

Antimicrobial resistance:

- Is an inevitable consequence of exposure to antibiotics
- reduces therapeutic options
- encourages increasingly broad spectrum empirical therapy
- is associated with increased morbidity, mortality and hospital costs